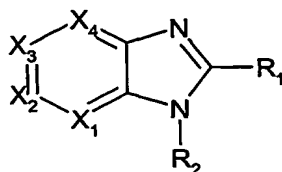


Claims

1. A compound of the general formula (I)



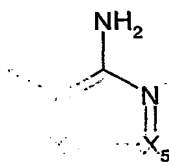
(I)

and physiologically acceptable salts and or N-oxides thereof wherein,

X_1 is N or CR_3 ; X_2 is N or CR_4 ; X_3 is N or CR_5 ; X_4 is N or CR_6 .

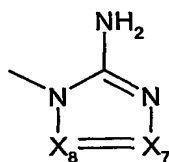
with the proviso that at least one but not more than two of X_1 , X_2 , X_3 and X_4 represents N.

R_1 is a 5-, or 6- membered heterocyclic group selected from group a, b, c or d



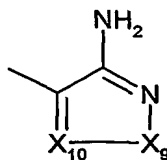
(a)

wherein X_5 is a group selected from N or CR_7 and X_6 is a group selected from O, S or NR_8 ;



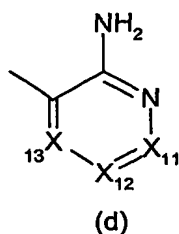
(b)

wherein X_7 and X_8 which may be the same or different is a group selected from N or CR_9 ;



(c)

wherein X_9 is a group selected from O, S or NR_8 and X_{10} is N or CR_{10} ;



wherein X_{11} , X_{12} and X_{13} may be the same or different and selected from a group N or CR_{11} ;

R_2 and R_8 independently represents hydrogen, hydroxy, aryl, heteroaryl, C_{3-7} cycloalkyl, heterocyclyl, a group YR_{12} , $N=R_{13}$, $CONR_{14}R_{15}$, $COCH_2NR_{19}R_{20}$, $NR_{14}COR_{16}$,

$SO_2NR_{14}R_{15}$ or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} cycloalkyl, heteroaryl, heterocyclyl, acylamino, NH_2 , $R_{19}NH$,

$R_{19}R_{20}N$, $SO_2NR_{14}R_{15}$, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $OalkNR_{19}R_{20}$, $SalkNR_{19}R_{20}$ or $NR_{17}SO_2R_{18}$];

R_3 , R_9 , R_{10} and R_{11} independently represent a group selected from hydrogen, halogen, hydroxy, $R_{19}O$, $R_{19}S(O)_n$, NH_2 , $R_{19}NH$, $R_{19}R_{20}N$, nitro, formyl, C_{1-4} alkanoyl, alkenyl (optionally substituted by optionally substituted phenyl, heterocyclyl, or

heteroaryl), carboxy, optionally substituted phenyl, heteroaryl, cycloalkyl, cycloalkylalkyl, aryloxy, heteroaryloxy, heterocyclyl, $CONR_{14}R_{15}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$,

$NR_{17}SO_2R_{18}$ or C_{1-6} alkyl [optionally substituted by a group selected from optionally substituted phenyl, C_{3-7} cycloalkyl, heteroaryl, heterocyclyl, NH_2 , $R_{19}NH$, $R_{19}R_{20}N$, acylamino, hydroxy, $CONR_{14}R_{16}$, $NR_{14}COR_{16}$, $SO_2NR_{14}R_{15}$, $NR_{17}SO_2R_{18}$,

$OalkNR_{19}R_{20}$, or $SalkNR_{19}R_{20}$ group];

R_{19} and R_{20} independently represent a group selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

Y represents O, NH , NR_{12} or $S(O)_n$;

R_{12} represents aryl, heteroaryl, cycloalkyl, heterocyclyl or C_{1-6} alkyl [optionally substituted

by a group selected from optionally substituted phenyl, C₃₋₇cycloalkyl, heteroaryl, heterocyclyl, NH₂, R₁₉NH, R₁₉R₂₀N, acylamino, hydroxy, CONR₁₄R₁₅, NR₁₄COR₁₈, SO₂NR₁₄R₁₅, NR₁₇SO₂R₁₈, OalkNR₁₉R₂₀, or SalkNR₁₉R₂₀ group];

R₁₃ represents an alkylidene group which may be substituted by an aryl, heteroaryl, heterocyclyl or cycloalkyl group or R₁₃ represents a cycloalkylidene or heterocycloalkylidene group.

R₁₄ and R₁₅ independently represent hydrogen, aryl, heteroaryl, cycloalkyl or C₁₋₆alkyl [optionally substituted by a group selected from optionally substituted phenyl, C₃₋₇cycloalkyl, heteroaryl, heterocyclyl, NH₂, R₁₉NH, R₁₉R₂₀N, or acylamino group] or R₁₄

and R₁₅ together with the nitrogen atom to which they are attached form a 4-7 heterocyclic ring which may be saturated or unsaturated and optionally contains another heteroatom selected from O, N or S(O)_n;

R₁₆ and R₁₈ independently represent, aryl, heteroaryl,

heterocyclyl, cycloalkyl or C₁₋₆alkyl [optionally substituted by a group selected from optionally substituted phenyl, C₃₋₇cycloalkyl, heteroaryl, heterocyclyl, NH₂,

R₁₉NH, R₁₉R₂₀N, or acylamino group] or the group NR₁₄R₁₅ wherein R₁₄ and R₁₅ have the meanings defined above;

R₁₇ represents hydrogen, aryl, heteroaryl, heterocyclyl, cycloalkyl or C₁₋₆alkyl [optionally substituted by a group selected from optionally substituted phenyl, C₃₋₇cycloalkyl,

heteroaryl, heterocyclyl, NH₂, R₁₉NH, R₁₉R₂₀N, or acylamino group];

Alk is a C₂₋₄ straight or branched alkylene chain

n is zero, 1 or 2.

2. A compound as claimed in claim 1 wherein only one of X₁, X₂, X₃ or X₄ represents N.

3. A compound as claimed in claim 2 wherein X₂ or X₃ represent N.

4. A compound as claimed in any of claims 1 to 3 wherein X₃ represents N

5. A compound as claimed in claim 1 wherein X₁ and X₃ each represents N.

6. A compound as claimed in any of claims 1 to 5 wherein R_1 is a group selected from (c) or (d).
7. A compound as claimed in any of claims 1 to 6 wherein R_1 is a group (c) in which X_9 is oxygen and X_{10} is nitrogen.
- 5 8. A compound as claimed in any of claims 1 to 7 wherein R_2 represents hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylmethyl, phenyl or phenyl substituted by(amino, dialkylamino, dialkylaminoalkylamino, alkyl, alkanoyl, alkoxy, halo, hydroxy, aminoalkyl, hydroxalkoxy, aminoalkoxy, alkylaminoalkoxy, N-alkyl-Nalkylaminoalkoxy, aminocarbonylalkoxy, alkylaminocarbonylalkoxy, dialkylaminocarbonylalkoxy, ureidoalkoxy, alkylureido, dialkylamino-acetamido, alkylthioalkoxy, phenylthioalkoxy, alkylsulphinylalkoxy, phenylsulphinylalkoxy, alkylsulphonylalkoxy, phenylsulphonylalkoxy, cyanoalkoxy, acylaminoethoxy, alkylsulphonylaminoalkoxy phenylsulphonylaminoalkoxy, alkoxy carbonylalkoxy, heterocyclalkoxy, heterocyclloxy, heterocyclyl), alkyl substituted by (alkoxy, amino, acylamino, $R_{19}NH$, $R_{19}R_{20}N$, a 4-7-membered heterocyclyl group, a 4-7 membered heterocyclyl group, a 5,6 fused bicyclic heteroaryl group, a 6,6 fused bicyclic heterocyclic group, a 6,5 fused heterocyclic group or a 6,7 fused heterocyclic group.
- 10 9 A compound as claimed in any of claims 1 to 8 wherein R_2 represents hydrogen, methyl, ethyl, isopropyl, sec butyl, 2-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropylmethyl, cyclohexylmethyl, phenyl, phenyl substituted by[amino, 4 - dimethylamino, dimethylaminoethylamino, N-methyl, dimethylaminoethylamino, N,N-bis(2-dimethylaminoethyl)amino), ethyl, acetyl, methoxy, 3-methylbutoxy, chlorine, bromine, hydroxy, aminomethyl, 2-hydroxyethoxy, 3-hydroxypropoxy, 2- aminoethoxy, 2-methylaminoethoxy, 2-dimethylaminoethoxy, 2 diethylaminoethoxy, 2 diethylamino-1-methylethoxy, 2-disopropylamino-1-methylethoxy, N N-benzyl N-methylaminoethoxy, aminocarbonylmethoxy, aminocarbonyl-2-methylethoxy, aminocarbonylethoxy, methylaminocarbonylmethoxy, dimethylaminocarboxymethoxy, ureidomethoxy, 3-
- 15 20 25

- methyleureido, dimethylaminoacetamido, methylthiomethoxy, phenylthiomethoxy, methylsulphinylmethoxy, phenylsulphinylmethoxy, methylsulphonylmethoxy, phenylsulphonylmethoxy, cyanomethoxy, 2-cyanoethoxy, t-butoxycarbonylaminoethoxy, isoxazolylaminoethoxy, isonicotinylaminoethoxy, methylsulphonylaminoethoxy,
- 5 phenylsulphonylaminoethoxy, 2-methoxycarbonyl 1-methylethoxy, morpholinoethoxy, piperidinoethoxy, 1-pyrrolidino-2-ylmethoxy, 1-methyl-piperidino-4-yloxy or 3-pyrrolidinyl, 2-hydroxy-1-methyl-ethyl, 3-aminopropyl, 4-aminobutyl, 5 aminopentyl, 4-butyloxycarbonylamino-butyl, 2-dimethylamino-1-methylethyl, 4-diethylamino-1-methyl-butyl, 3-dimethylaminopropyl, 4-methylpiperazin-1-ethyl, 2-piperazin-yl-ethyl, piperidine 4-yl
- 10 methyl, piperidine 3-yl methyl, piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, 5-indazolyl or 6-indazolyl, tetrahydroisoquinolin-5-yl, 2-methyl tetrahydroisoquinolin-7-yl, 2-methanesulphonyl-tetrahydroisoquinolin-7-yl, tetrahydroisoquinolin-7-yl, 3,4 dihydro-2H-isoquinolin-1-one-7-yl, 2,3-dihydro-1H-isoindol-5-yl, benzo{1,3}dioxol-5-yl or 2,3,4,5-tetrahydro-1H-benzo[c]azepin-8-yl
- 15 10 A compound as claimed in any of claims 1 to 9 wherein R₃ represents hydrogen, halogen, hydroxy, carboxyl, phenyl or phenyl (substituted by one or two groups selected from alkoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminoalkyl, alkyl, carboxyl carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy,
- 20 CH₃S(O)_n wherein n is zero, 1 or 2, CH₃SO₂NH, or halogen), or heterocyclyl, heteroaryl, 6,5-fused bicycloheterocyclyl, an optionally substituted phenyl substituted by the group CH₂NR₁₉R₂₀ wherein R₁₉ is alkyl, phenyl or a heterocyclic group and R₂₀ is hydrogen or methyl, or NR₁₉R₂₀ is a 4-7 heterocyclic group, alkyl substituted by (a 4-7 membered heterocyclyl group or a group NR₁₉R₂₀ (wherein R₁₉ is hydroxylalkyl, optionally substituted
- 25 benzyl, C₃₋₇ cycloalkyl, a heterocyclic group, a 4-7 membered heterocyclalkyl or C₃₋₇ cycloalkylalkyl, R₂₀ is hydrogen, methyl or acetyl),

4-heterocycloxy, heterocyclalkyloxy, vinyl (optionally substituted by optionally substituted phenyl), $\text{CONR}_{14}\text{R}_{15}$

wherein R_{15} is hydrogen, R_{14} is benzyl, phenethyl, aminoalkyl, 4-7 membered heterocycl or 4-7 membered heterocyclalkyl, or R_{14} and R_{15} together with the nitrogen atom to which they are attached represent a 4-7 membered heterocycl group, a group $\text{R}_{19}\text{S}(\text{O})_n$ (wherein n is zero, 1 or 2 and R_{19} is optionally substituted phenyl), or a group R_{19}NH and R_{19} is optionally substituted phenyl or heteroaryl.

11 A compound as claimed in any of claims 1 to 10 wherein R_3 represents hydrogen, bromine, hydroxy, carboxyl, phenyl or phenyl (substituted by one or two groups selected

10 from methoxy, ethoxy, hydroxy, hydroxymethyl, trifluoromethyl, trifluoromethoxy, amino, acetamido, aminomethyl, aminoethyl, methyl, ethyl, carboxyl, carboxamido, N,N-dimethylcarboxamido, cyano, formyl, phenoxy, $\text{CH}_3\text{S}(\text{O})_n$ wherein n is zero, 1 or 2, $\text{CH}_3\text{SO}_2\text{NH}$, or fluorine), 5-methyl-1,2,4-oxadiazol-3-yl, 2-thienyl, 4-methylthienyl, 5-

15 3,5-dimethylphenyl, 4-methylphenyl, or 3-thienyl, 2-furanyl, pyridyl such as 3-pyridyl or 4-pyridyl, 3,5-dimethylphenyl, 4-methylphenyl, or 8-quinolyl, benzothienyl, 5-benzo[1,3]dioxolyl, a phenyl or fluorophenyl substituted by the group $\text{CH}_2\text{NR}_{19}\text{R}_{20}$ (wherein $\text{NR}_{19}\text{R}_{20}$ represents

ethylamino, dimethylamino, 4-morpholino, pyrrolidino, piperidino, piperidin-4-yl-amino or 1-t butoxycarbonyl-piperidin-4-yl-amino.), 3-hydroxypropylamino, 4-bromobenzylamino, 4-methoxybenzylamino, 4-piperidinylaminomethyl, N-4-piperidinyl-N-methylaminomethyl, 1-t
20 butoxycarbonyl-piperidinyl-aminomethyl

4-aminopiperidinomethyl, 1,4-diazepan-1-ylmethyl, piperazinomethyl, 4-methylpiperazinomethyl, 4-acetylpiperizin-1-ylmethyl, 4-ethylpiperazinomethyl
4-morpholinomethyl, piperidinomethyl, 4-(methylamino)piperidinomethyl, 4-cyclopropylaminopiperidinomethyl, pyrrolidinomethyl, 3-dimethylaminopyrrolidinomethyl, 2-hydroxymethylpyrrolidinomethyl, 4-ethylpiperazino-methyl, 3-pyrrolidin-1-yl-propylaminomethyl, 4-(4-fluorophenyl) piperazinomethyl, 3-piperidinyl-1-yl-propylaminomethyl, 3-morpholin-4-yl-propylaminomethyl, 3-(4-methylpiperazin-yl

propylaminomethyl, 1-methyl piperidin-4-yl-aminomethyl, 4-pyrrolidinocarbonylmethyl-
 piperazinomethyl, 2-pyrrolidin-1-ylmethylpyrrolidinomethyl, 2-pyrrolidin-1-yl-
 ethylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 1-methyl-piperidin-4-ylaminomethyl, 1-
 isopropyl-piperidin-4-ylaminomethyl, 3-dimethylaminopyrrolidinomethyl, 2-(morpholin-yl-
 5 methyl)-pyrrolidinomethyl, 3-piperidin-1-yl-propylaminomethyl, 3-morpholin-4-yl-
 propylaminomethyl, 3-(4-methylpiperazin-1-ylpropylaminomethyl, piperidin-1-
 ylmethylpyrrolidinomethyl, 3,5-dimethylpiperazinomethyl, pyrrolidin-1-ylpiperidinomethyl,
 pyrrolidino-3-ylaminomethyl, pyrrolidin-2-ylmethylaminomethyl,
 4-aminomethylcyclohexymethylaminomethyl, 4-aminocyclohexylaminomethyl, 2-piperazin-1-
 10 ylethylamoinomethyl, 3-amino-pyrrolidinomethyl, pyrrolidino-2-ylmethylaminomethyl,
 piperidin-4-ylmethylaminomethyl, 4-aminomethylpiperidinomethyl, 4-
 (cyclopropylaminopiperidinomethyl,
 3-(piperazino-1-yl) propylaminomethyl, 2-(morpholin-4ylmethyl)pyrrolidinomethyl
 2-(piperidin-1-ylmethyl)pyrrolidinomethyl, 2-(piperazin-1-ylmethyl)pyrrolidinomethyl,
 piperidin-4-ylmethyl, N-piperidin-4-yl-acetamidomethyl, piperidin-4-yloxy, or piperidin-4-
 ylmethyloxy,
 4-methyloxystyryl, CONR₁₄R₁₅
 wherein R₁₅ is hydrogen, R₁₄ is benzyl, phenethyl, 3-aminopropyl, 4-aminobutyl, 6-
 aminoethyl, 3 or 4-piperidinyl 1-aminomethylcarbonyl-piperidin-4-yl, 3-pyrrolidinyl, piperidin-
 20 2-ylmethyl or piperidin-4-ylmethyl, morpholin-2-ylmethyl or piperazinoethyl, or R₁₄ and R₁₅
 together with the nitrogen atom to which they are attached represent piperazino, 1-
 methylpiperazino, 4-(2-aminoethyl)piperazino, 4-(t-butoxycarbonylaminoethyl)piperazino, 4-
 aminomethylcarbonylpiperazino, 4-aminoethylcarbonylpiperazino, 4-1-
 (aminoethylcarbonylpiperazino, 4-(1-methylaminoethylcarbonylpiperazino, 4-pyrrolidin-2-yl-
 25 carbonylpiperazino, pyrrolidino, 3-aminopyrrolidino, 2-methoxycarbonylpyrrolidino,
 morpholino, 2 (pyrrolidin-1yl)methyl pyrrolidino, a group R₁₉S(O)_n wherein n is zero, and

R₁₉ is phenyl optionally substituted by methoxy, a group R₁₉NH wherein R₁₉ is phenyl, 4-morpholinophenyl or 3-aminopyridyl.

12 A compound as claimed in any of claims 1 to 11 wherein R₄ is hydrogen, methyl,
5 methoxy, methylthio, phenylamino or phenoxy optionally substituted by fluorine or acetamido.

13 A compound as claimed in any of claims 1 to 12 wherein R₅ is hydrogen, methyl, methoxy or phenoxy.

14 A compound as claimed in any of claims 1 to 13 wherein R₆ is hydrogen, chlorine ,
10 hydroxymethyl, methyl, methoxy, phenyl, 1- pyrrolidinyl or 1- pyrazolyl.

15 A pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt and or an N oxide thereof together with one or more pharmaceutically acceptable excipients and /or carriers .

16 A compound of formula (I) and/or physiologically acceptable salts thereof for use in
15 therapy .

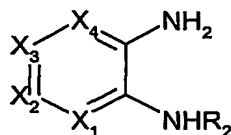
17 The use of a compound of formula (I) and/or a physiologically acceptable salt thereof in the manufacture of a medicament for inhibiting the effects of the kinase Msk-1 and or Rho-kinase 1 and or 2.

18 A method for inhibiting the effects of the kinase MSK-1 and or Rho-kinase 1 and or 2
20 comprising administering to a patient in need thereof an effective amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

19 A process for preparing a compound of formula (I) which comprises :-

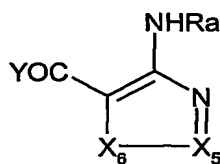
a) a process for preparing compounds of formula (I) wherein R₁ is a group (a), (c)
and

25 (d) by reacting the diamine (II)

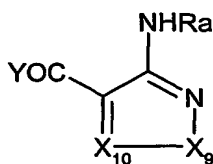


(II)

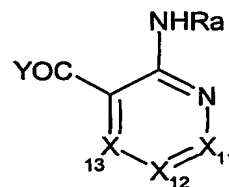
wherein R_2 , X_1 , X_2 , X_3 and X_4 have the meanings defined in (I) with the appropriate compound of formula (III), (IV) or (V)



(III)



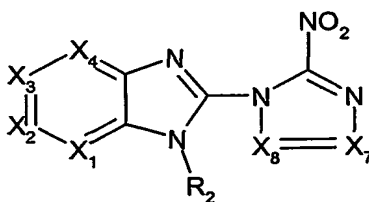
(IV)



(V)

wherein Y is hydrogen, halogen e.g. Cl, Br or I, hydroxy or C_{1-4} alkoxy, Ra is hydrogen or a nitrogen protecting group such as an alkoxycarbonyl or benzyloxycarbonyl group and each of X_5 , X_6 , X_9 , X_{10} , X_{11} , X_{12} and X_{13} have the meanings as defined in formula (I) or is a group available thereto, followed when required by a nitrogen protecting group Ra using conventional methods.

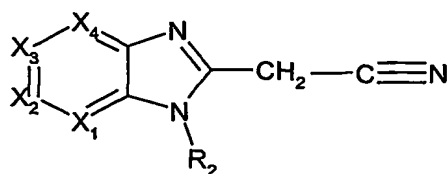
b) a process for preparing compounds of formula (I) wherein R_1 is the group (b) reducing of the corresponding nitro derivative (VI)



(VI)

wherein R_2 , R_3 , R_3 , X_1 , X_2 , X_3 , X_4 , X_7 and X_8 have the meanings defined in formula (I).

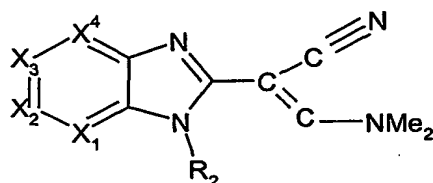
c) a process for the preparation compounds of formula (I) wherein R_1 is the group (c) and X_9 is oxygen and X_{10} is nitrogen may be prepared by reacting the nitrile (VII)



(VII)

wherein R_2 , X_1 , X_2 , X_3 and X_4 have the meanings defined in formula (I) with hydrochloric acid and sodium nitrite in a solvent and treatment of the product thus formed with a and hydroxylamine.

- 5 d) a process for preparing a compounds of formula (I) wherein R_1 represent the group (c) and wherein X_9 is NH and X_{10} is CH may be prepared by reacting compound (VIII)



(VIII)

wherein R_2 , X_1 , X_2 , X_3 and X_4 have the meanings defined in formula (I) with hydrazine.

- 10 and if necessary or desired:-

- i removal of any protecting groups
- ii converting one compound of the invention into another
- iii isolating the product of the reaction as a salt and or a solvate thereof

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.